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(54) Title: USE OF MELATONIN FOR TREATING PATIENTS SUFFERING FROM DRUG ADDICTION

(57) Abstract

Melatonin is used in the manufacture of a medicament for treating a multidrug addict, or a patient who has symptoms of having become dependent on, tolerant of, or addicted to a benzodiazepine drug, or for treating a patient who has been clinically diagnosed as having a condition susceptible to alleviation by administration of a benzodiazepine drug, while simultaneously preventing the occurrence in the patient of symptoms of dependence on, tolerance of, or addiction to said benzodiazepine drug. The invention further relates to a pharmaceutical formulation for the above-stated purposes, which comprises at least one diluent, carrier or adjuvant and as active ingredients a benzodiazepine drug and melatonin.

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USE OF MELATONIN FOR TREATING PATIENTS SUFFERING FROM DRUG ADDICTION

The present invention relates to melatonin for use in the manufacture of a medicament for treating, or for preventing, symptoms of dependence on, tolerance of, or addiction to benzodiazepine drugs, for treating multidrug addicts and to a pharmaceutical formulation, for use in such treatments

Dependence on benzodiazepines often develops in insomniacs who use them for the induction of sleep and in multi-drug addicts who in the process of withdrawal from narcotics, become addicted to benzodiazepines to ease anxiety and convulsions. Moreover, chronic benzodiazepine administration (where the benzodiazepines usually have long half-life values) may induce tolerance, expressed by an ineffective increase in dosage, by an unknown mechanism. Furthermore, rebound or "withdrawal" phenomena which often follow abrupt cessation of these drugs, as observed both in animals and humans lead to addiction (Greenblatt, D.J., and Shader, R.I., Drug Metab. Rev., 1978, 8: 13-28). In the 1990 US National Household Survey of the Use of Psychotherapeutic Medications, about 8% of the medical users of hypnotics advanced a prescribed dose on their own, which is an increase of 25% as compared to former report in 1979. Taking into consideration that the survey found that 2.6% of the US population took benzodiazepine hypnotics (as compared to 2.4% in 1979) the number of individuals in the US only who do develop tolerance and dependence may be estimated at 560,000. These values do not include substance use outside medical or social norms and multiple drug abuse. No method of rapid

withdrawal followed by an effective alternative treatment has yet been reported in patients who developed dependence on benzodiazepine hypnotics and this problem is a great obstacle in the rehabilitation and recovery of narcotic drug addicts.

It is well known that melatonin, an indole-derived hormone produced at night by the pineal gland, plays a major role in mediating the circadian sleep-wake cycle and in the regulation of sleep. There is also some evidence that melatonin can increase benzodiazepine efficacy, see, e.g., Cardinali, D.P. et al, Adv. Biochem. Psychopharm., 1986, 42: 155- 164; Acuna Castroviejo, D., et al, J. Pineal Res., 1986, 3: 101-102; and Niles, L.P. et al, J. Neural Transm. 70: 117-124]. Also, melatonin can enhance the anxiolytic effects of diazepam in mice (Guardiola-Lemaitre, B. et al, Pharmacol. Biochem. Behav., 1992, 41, 405-4080). On the other hand, it has been suggested that benzodiazepines could, in some species including humans, potentiate GABA-induced inhibition of melatonin synthesis and secretion (McIntyre, I.M. et al, Biol. Psychiat., 1988, 24: 105-108) and that nocturnal enhancement of plasma melatonin could be suppressed by benzodiazepines in humans, thus leading to distortion in the diurnal melatonin rhythm (Kabuto, M. et al, Endocr. Japon., 1986, 33, 405-414). Moreover, it has been observed that chronic treatment with oxazepam modified the diurnal variations in the density of melatonin receptors at night in the rat brain and that this effect was not observed in pinealectomized animals (Anis, Y. et al, J. Neural Transm., 1992, 89: 155-166).

It has surprisingly been found in connection with the

present invention that administration of melatonin concurrently with benzodiazepine drugs can potentially (1) wean a patient away from dependence on, addiction to, or tolerance of such drugs, and (2) in the case of a patient who has been diagnosed as requiring a benzodiazepine drug (where such undesirable symptoms have not yet occurred), prevent the occurrence of such symptoms.

DESCRIPTION OF THE INVENTION

The present invention thus provides in one aspect, use of melatonin in the manufacture of a medicament for treating a multidrug addict, or a patient who has symptoms of having become dependent on, tolerant of, or addicted to a benzodiazepine drug, or for treating a patient who has been clinically diagnosed as having a condition susceptible to alleviation by administration of a benzodiazepine drug, while simultaneously preventing the occurrence in the patient of symptoms of dependence on, tolerance of, or addiction to said benzodiazepine drug.

In another aspect, the present invention provides a pharmaceutical formulation, for use in treating a multidrug addict, or a patient who has symptoms of having become dependent on, tolerant of, or addicted to a benzodiazepine drug, or for treating a patient who has been clinically diagnosed as having a condition susceptible to alleviation by administration of a benzodiazepine drug, while simultaneously preventing the occurrence in the patient of symptoms of dependence on, tolerance of, or addiction to said benzodiazepine drug, which comprises at least one diluent, carrier or adjuvant and as active ingredients a benzodiazepine drug and melatonin.

The said medicament may be a pharmaceutical formulation adapted for oral, rectal, parenteral or transdermal administration and which comprises at least one diluent, carrier or adjuvant, and may be additionally characterized by at least one of the following features: (i) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 0.0025-100 mg; (ii) it is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate; (iii) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier. The medicament may comprise also, and the pharmaceutical formulation according to the invention comprises, at least one benzodiazepine drug, such as at least one of Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Flunitrazepam, Flurazepam, Halazepam, Lorazepam, Oxazepam, Prazepam, Temazepam and Triazolam. The formulation which comprises at least one benzodiazepine drug may also be characterized further by one or more of the features (i), (ii) and (iii) as described above.

In applying the present invention to treating a multidrug addict or a patient who has symptoms of having become dependent on, tolerant of, or addicted to a benzodiazepine drug, administration of a benzodiazepine drug to the patient is continued, at least initially, and melatonin is concurrently administered to the patient an amount which is effective to alleviate at least one of such symptoms.

In a particular embodiment of such treatment, either

one of the benzodiazepine drug and the melatonin may be in the form of a pharmaceutical formulation adapted for oral, rectal, parenteral or transdermal administration and which comprises at least one diluent, carrier or adjuvant. Alternatively, benzodiazepine drug and melatonin may each be administered thus formulated, either separately, or may be combined into a single pharmaceutical formulation including both diazepine drug and melatonin.

In relation to the administration of the melatonin, whether administered separately from or together with one or more benzodiazepine drugs, administration may be effected at a daily dosage rate which e.g. lies within the range of 0.01-100 mg; it may be administered in the form of a controlled release formulation. Illustratively, 1-2 mg melatonin in the form of a controlled release formulation may be administered at night. The melatonin may be administered together with a melatonin receptor modifier or a melatonin profile modifier. Examples of melatonin receptor modifiers are short-acting benzodiazepines such as Oxazepam; examples of melatonin profile modifiers are benzodiazepines, beta-blockers and serotonin uptake inhibitors. Instead of, or in addition to, use of such a profile modifier, the melatonin profile may be modified by subjecting the patient to the effect of light, before, after or during administration of melatonin.

The benzodiazepine drugs referred to herein may give rise to symptoms of dependence, tolerance and/or addiction. Without prejudice to this generality, such drug or drugs may be

one or more of, e.g., Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Flunitrazepam, Flurazepam, Halazepam, Lorazepam, Oxazepam, Prazepam, Temazepam and Triazolam, as indicated above.

In one alternative embodiment of applying the invention to treating the above-mentioned symptoms, the benzodiazepine drug(s) is(are) initially continued to be administered to the patient, concurrently with the melatonin, at a daily rate substantially the same as that received by the patient prior to commencing treatment with melatonin. In another alternative embodiment of applying the invention in treating such symptoms, the benzodiazepine drug(s) is(are) administered to the patient, concurrently with the melatonin, at a progressively decreasing daily rate compared with that received by the patient prior to commencing treatment with melatonin. In this embodiment, the progressively decreasing daily rate of administration may be continued, e.g., until a predetermined stabilized rate of administration is achieved, or alternatively, e.g., until the amount of benzodiazepine drug administered is zero.

In applying the invention for preventive purposes, i.e. in treating a patient who has been clinically diagnosed as having a condition susceptible to alleviation by administration of a benzodiazepine drug, while simultaneously preventing the occurrence in the patient of symptoms of dependence on, tolerance of, or addiction to said benzodiazepine drug, a benzodiazepine drug is administered in an amount effective to alleviate said condition, while concurrently administering to the patient an amount of melatonin which is effective to prevent at least one of

such symptoms. The various embodiments described above as applicable to treating a patient having the stated symptom(s) are also correspondingly applicable to preventive purposes, except insofar as they will not be applicable for reasons which are self-evident to a person of the art, e.g. in this instance treatment with a benzodiazepine drug is a desideratum, so that evidently the amount of benzodiazepine administered, while possibly being reduced in any particular case as determined by a physician, will not be reduced to zero.

However, it will be within the scope of the preventive application of the invention, not only to administer, concurrently with melatonin, the benzodiazepine drug(s) at the conventional daily dosage rate to achieve a particular purpose, but in the alternative to similarly administer such drug(s) at a daily rate which is less than that which is conventionally administered to a patient in order to alleviate said condition.

As stated above, the invention also extends to a pharmaceutical formulation which includes at least one a benzodiazepine drug and melatonin. Since benzodiazepine drugs are usually administered 1-4 times daily, a daily rate of 0.01-100 mg melatonin, administered typically at night, in the same formulation as the benzodiazepine(s), or even if administered separately therefrom, will illustratively be achieved by administering benzodiazepines as follows:

days	unit dosage of benzodiazepines within the range
1	0.01 -100 mg
2	0.05- 50 mg
3	0.033- 33.3 mg
4	0.025- 25 mg

Thus, when the pharmaceutical formulation of the invention is in unit dosage form, each dosage unit is preferably administered at night and preferably comprises an amount of melatonin within the range 0.0025-100 mg.

The following Table gives the amounts of benzodiazepine drugs used for treating the stated conditions in adults. For further information, e.g. as to reservations, half-life, forms of administration and suitable dosages for children or infants, see Goodman & Gilman's "The Pharmacological Basis of Therapeutics", 7th Edition, 1985 (MacMillan Publishing Co.), the passages relating to use of benzodiazepines (e.g. pp. 352, 437), all of which passages are incorporated herein by reference.

Benzodiazepine	Content of unit oral dosage mg (x per day) Sedative	Hypnotic	Usual daily oral dose*, Anxiolytic
Alprazolam			0.75-1.5
Chlordiazepoxide	10-100 (1-3)	50-100	15- 40
Clorazepate	3.75-15(2-4)	15- 30	30
Diazepam	5- 10 (3-4)	5- 10	4- 40
Flurazepam		15- 30	
Halazepam			60-160
Lorazepam		2- 4	2- 6
Oxazepam	15- 30 (3-4)	15- 30	30- 60
Prazepam			20- 40
Temazepam		15- 30	
Triazolam		0.25-0.5	

*mg, generally divided into 2-4 unit doses; for further information including parenteral dosage rates, see Goodman & Gilman, loc cit

The preparation and release profile of formulations for use in accordance with the invention or its applications are illustrated below.

(a) There were compressed in a 7 mm cylindrical punch at 2.5 tons, after dry mixing of the powdered materials, namely 2 mg/tablet melatonin (Biosynth Co., Switzerland) and acrylic resin carrier (Rohm Pharma), which was Eudragit RS100 (formulation SR-Ms) or Eudragit RSPO (formulation SR-Mf), besides other components as noted: formulation SR-Ms: Eudragit RS100 48.8%, lactose 50%, melatonin 1.2%; formulation SR-Mf: Eudragit RSPO 35.3%, lactose 16.7%, calcium hydrogen phosphate 41.4%, talc 1.3%, magnesium stearate 4%, melatonin 1.3%. SR-Ms and SR-Mf are sustained release formulations.

A conventional dosage form (RM) was prepared similarly to formulation SR-Mf, but using lactose in place of Eudragit as carrier.

(b) The potential release profile of the tablets prepared as described in paragraph (a), was first investigated by in vitro dissolution of melatonin therefrom in distilled water at 37°C. The results in Table A show the % of the melatonin content (mean value of 6 tablets) which has dissolved at the stated intervals of time.

Table A

Time(hours)	1	2	4	6	8	10
melatonin (%) released from:						
SR-Ms	12	29	62	84	90	100
SR-Mf	32	51	76	88	100	
RM	93	96	100			

(c) The in vivo profile of the SR-Mf tablets prepared as described in paragraph (a), was investigated by oral administration twice to a healthy male (age 36) at 10 a.m., i.e. when circulating melatonin levels are undetectable. The amount of melatonin released in vivo was determined by radioimmunoassay of its major metabolite, 6-sulphatoxymelatonin, in the urine. The amount of urinary 6-sulphatoxymelatonin closely reflects the blood level of the hormone. The results in Table B show the melatonin determined as a % of the total melatonin administered (mean value of 2 tablets).

Table B

In vivo release of melatonin from SR-Mf

Time(hours)	1	2	4	6	8	10
% release at intervals	10.7	25.7	40.6	14.0	7.0	1.9
cumulative release %	10.7	36.4	77.0	91.0	98.0	99.9

It is noted that the release of melatonin in vitro, illustrated in Table A, provides only an approximate indication of the in vivo release profile due to the known phenomenon of the active compound being absorbed by the tissues in the early stages of release.

The amount of melatonin in the sustained release formulations may be changed e.g. to 0.5, 1 or 5 mg/tablet, without affecting the release pattern found for the tablets containing 2 mg/tablet melatonin.

Insofar as analogues of melatonin which substantially imitate the function of melatonin in the human body are known in the art, it will be appreciated that such analogues are deemed to be obvious chemical equivalents of melatonin, in the present context.

In accordance with the present invention, one or more benzodiazepines may be incorporated in the above formulations, in amounts which have been described herein.

The invention will now be illustrated by the following Examples.

EXAMPLE 1

The reciprocal effects of chronic benzodiazepine and melatonin administration on brain melatonin and benzodiazepine receptors and the ability of melatonin to reverse these effects were studied. Male rats were maintained on a daily 14 h light:10 h darkness schedule (lights-on 05.00h; cool white fluorescent illumination) at 24±2°C. Food and drinking water were supplied ad libitum. The animals (2 months old), were divided into 4 groups, 5 animals in each. The animals in one group (CON) were injected i.p. daily at 16:00 h with vehicle (200 µl saline). Those in the second group (VAL) were injected daily, i.p. at 16:00 h with diazepam (1 mg in 200 µl vehicle; Roche). The animals of the third group (MEL) were injected daily at 16:00 h with vehicle; the drinking water of this group contained melatonin (4 mg dissolved in 100 µl ethanol and diluted to 1 liter). The animals in the fourth group (VAL/MEL) were injected daily at 16:00 h with diazepam (1 mg in 200 µl vehicle); the drinking water of this group contained melatonin (4 mg dissolved in 100 µl ethanol and diluted to 1 liter). After 21 days the treatment was stopped and the animals were weighed. The mean body weight values in the VAL (274±20 g) and VAL/MEL groups (239±30 g) were found to be slightly lower than those in CON (292±30 g) or MEL groups (285±30 g).

The animals were decapitated between 18-19.00 h of the next day (at this time the density of 2-^{125}I-iodomelatonin in the medulla pons should be maximal); their brains were rapidly removed and crude synaptosomal pellets were prepared as

described, and melatonin receptors were assessed, as described by Laudon, M. and Zisapel, N., FEBS Lett., 1986, 197: 9-12. Benzodiazepine receptors were assessed by measuring ^{3}H-flunitrazepam (^{3}H-FNZ) and ^{3}H-RO 15-1788 binding as described by Amiri, Z. et al, Brain Res., 1991, 553: 155-158. Binding parameters were calculated from the equilibrium binding data. Bmax values represent the specific binding of 2-^{125}I-iodomelatonin, ^{3}H-FNZ or ^{3}H-RO 15-1788 at saturation, and Kd values are the apparent dissociation constants. Binding parameters of the various groups were compared by analysis of Variance followed by Student-Newman-Keul's test for multiple comparisons. Differences were considered significant if $P<0.05$. Daily injections of diazepam (1 mg i.p at 16.00 h) to male rats for 3 weeks markedly reduced the density of 2-^{125}I-iodomelatonin binding sites in the medulla-pons (Table 1), whereas benzodiazepine binding was not significantly affected (Table 2). If melatonin receptors are related to the control of the sleep-wake cycle, the results suggest that chronic benzodiazepine administration results in the diminution of melatonin-responsive mechanisms and consequent physiological activities.

Melatonin, given orally via the drinking water for 3 weeks, significantly enhanced ^{3}H-RO 15-1788 binding in the medulla pons (Tables 2,3), whereas 2-^{125}I-iodomelatonin binding was not affected. The increase in benzodiazepine binding site density and apparent Kd in the medulla-pons induced by the melatonin treatment, is compatible with the augmentation observed previously in the rat cortex, and shown to be mediated by opioid

peptides (Gomar, M.D. et al, Neuroendocrinology 1993, 4:987-990). The fact that this enhancement persists even in diazepam-treated animals may rule out competition between melatonin and benzodiazepines on the benzodiazepine binding sites.

Daily administration of both diazepam and melatonin, enhanced ^{3}H-RO 15-1788 binding in the medulla pons, and reversed the diazepam-induced suppression of 2-^{125}I-iodomelatonin binding in this area (Tables 1,2). These results are surprising since as previously shown (Anis, Y. et al, in melatonin binding sites in the hamster brain: impact of melatonin. Molec. Cell. Endocrinol., 1989, 67: 121-128; Oaknin-Bendahan, S. et al, J. Basic Clin. Physiol. Pharmacol., 1992, 3: 253-268) and is also confirmed in the present study, administration of melatonin by morning or evening injections, or orally via the drinking water, does not affect the density or diurnal variations in melatonin binding sites in most brain areas including medulla-pons. Moreover, pinealectomy does not abolish the diurnal variations in 2-^{125}I-iodomelatonin binding sites although it affects their phase position (Oaknin-Bendahan et al., 1992, ibid). Thus, changes in melatonin binding site densities might not be due to autoregulation of the receptor by melatonin.

In the cerebral cortex, melatonin slightly reduced ^{3}H-RO 15-1788 and ^{3}H-FNZ binding. Diazepam treatment did not significantly affect ^{3}H-RO 15-1788 and ^{3}H-FNZ binding but prevented the melatonin-mediated decrease (Tables 2,3). These data suggest firstly, that the effects of melatonin on benzodiazepine binding sites are localized, rather than general

suppression or facilitation of the binding occurring, and secondly, that melatonin replacement therapy may counteract some deleterious effects of chronic benzodiazepine treatment.

Table 1 shows equilibrium binding parameters of 2-^{125}I-iodomelatonin binding sites in synaptosomal preparations from the medulla-pons area of diazepam and/or melatonin-treated and untreated rats, in terms of mean and S.D. values of Kd (in nM) and Bmax (in µmol/mg protein). Values denoted by the same character In Table 1 do not differ significantly. (Codes having the same significance are also used in Tables 2 and 3, below.)

Table 1

GROUP	Kd±sd	Bmax±sd
CON	0.87±0.2 a	7.9±1.0 a
MEL	1.16±0.3 a	7.7±1.0 a
VAL	0.98±0.21 a	5.1±0.5 b
VAL/MEL	2.27±0.75 b	12.5±2.0 c

Table 2 shows equilibrium binding parameters of ^{3}H-RO 15-1788 binding sites in synaptosomal preparations from the medulla-pons area of diazepam and/or melatonin-treated and untreated rats, in terms of mean and S.D. values of Kd (in nM) and Bmax (in µmol/mg protein).

Table 2

GROUP	Kd±sd	Bmax±sd
CON	2.3±0.4 a	310±22 a
MEL	2.8±0.2 a	476±26 b
VAL	2.5±0.4 a	295±34 a
VAL/MEL	2.6±0.5 a	375±87 b

Table 3 shows the effect of diazepam or melatonin on ^{3}H-FNZ and ^{3}H-RO 15-1788 binding in rat cerebral cortex membranes, in terms of mean and S.D. values (in µmol/mg protein).

Table 3

GROUP	^{3}H-FNZ	^{3}H-RO 15-1788
CON	935±31 a	1354± 48 a
MEL	765±78 b	1060± 26 b
VAL	870±22 a	1264± 99 a
VAL/MEL	980±16 a	1362±155 a

EXAMPLE 2

This Example illustrates the surprising action of melatonin in facilitating very rapid withdrawal from benzodiazepine drug tolerance. A 43 year old female, married with 2 children has been suffering from sleep onset insomnia for the last 10 years accompanied by frequent and severe migraine attacks. A thorough neurological assessment was negative. Psychiatric or other organic problems were also ruled out. Throughout these years she had been treated with benzodiazepines, tricyclic antidepressants and neuroleptic drugs,

as well as by biofeedback and relaxation methods, with no apparent relief. For the last year she has been using 4-8 mg Lorazepam every night.

A thorough psychological assessment at the Sleep Laboratory of Tel Aviv University, did not disclose any significant pathology. The quality of sleep was assessed by an actigraph tracing which automatically monitors the bedtime sleep-wake pattern through a small device attached to the hand wrist. The tracing was recorded for 3 consecutive days and showed a deranged sleep pattern: reduced efficiency, long sleep latency and multiple waking episodes. Urine was collected every 3 hours (for 36 hours) and assayed for the major melatonin metabolite: 6-sulphatoxymelatonin, as an indicator for the diurnal secretion of plasma melatonin. Results showed that 6-sulphatoxymelatonin excretion levels were lower than for aged-matched individuals, and lacked the typical circadian rhythm (TABLE 4).

Oral administration of a controlled-release melatonin formulation in the form of tablets containing 1 mg melatonin (Neurim Pharmaceuticals, Israel) was initiated, in order to correct for the deficiency and distortion of the melatonin rhythm. One tablet was administered daily at 8:30 p.m. The patient was asked to gradually reduce the number of benzodiazepine tablets taken each night. Surprisingly, within 2 days, the patient stopped using the benzodiazepine hypnotics altogether, and claimed that her insomnia has improved remarkably. In addition, her headaches also subsided gradually. A repeated actigraph tracing after 3 weeks treatment showed marked

improvement in sleep pattern.

The treatment was stopped and 2 weeks afterwards urine was collected again every 3 hours (for 36 hours) and assayed for 6-sulphatoxymelatonin. The results (Table 4) indicated an increase in amount and a clear nocturnal peak of urinary 6-sulphatoxymelatonin. A 5-month follow-up has confirmed that the patient still maintains her quality of sleep and hardly suffers from headaches. After 6 months without treatment sleep quality began to deteriorate and melatonin therapy was resumed.

This case-report indicates potentially a breakthrough in relieving many patients whose quality of life has been impaired by addiction to benzodiazepine hypnotics. Administration of exogenous melatonin may moreover serve as a means of rapid and symptomless withdrawal from benzodiazepines in tolerant patients.

Table 4: Urinary 6-sulphatoxymelatonin in benzodiazepine -dependent patient before and after melatonin therapy (µg/hour)

Time	before treatment	after treatment
15.00	0.3	0.11
18.00	0.16	0.45
21.00	0.18	0.11
24.00	0.13	1.24
3.00	0.23	0.74
6.00	0.23	0.36
9.00	0.22	0.21
12.00	0.13	0.01
15.00	0.22	0.04

EXAMPLE 3

This example illustrates the effects of long term administration of melatonin in the treatment of insomnia in patients dependent on a benzodiazepine drug.

Two volunteers, Y.L., an 80 year old male, and E.L., a 73 year old female, had each suffered for a number of years from insomnia and/or frequent awakenings during the night, accompanied by difficulty in resuming sleep afterwards. Both were found to have low melatonin secretion, by determination of the amount of the metabolite 6-sulphatoxymelatonin, in the urine. Both patients had been taking 1-2 mg of flunitrazepam orally prior to retiring each evening.

Each patient was weaned off the flunitrazepam by gradually reducing the dose and simultaneously administering melatonin orally (2 mg melatonin daily in controlled release form) over a two-month period. Since the end of that period, each patient has continued taking melatonin in the same form and at the same dosage rate over approximately two years.

Each patient has subjectively reported good sleep inducement and a substantial improvement in sleep quality. Specifically, patient E.L. noted an improvement in sleep quality at the beginning of the weaning period and Y.L. noted a similar effect about two weeks into the weaning period. Each patient reported reduced fatigue during the daytime within several days after the beginning of the weaning period, and also indicated that the melatonin has caused neither residual tiredness in the morning, nor any hangover feeling. No side effects were reported

by either patient.

EXAMPLE 4

This example, designed as a randomized, double-blind, crossover study, illustrates the ability of melatonin replacement therapy to improve sleep maintenance in chronic benzodiazepine drug-using elderly patients.

The group, of mean age 78 (SD=9.7) consisted of eight men and five women, all of whom complained of long-term insomnia and used various benzodiazepines for sleep induction. Urine was collected approximately every 4 hours for 15 hours and the nocturnal excretion of 6-sulphatoxymelatonin, the major urinary metabolite of melatonin, was assayed in duplicate by RIA. Urine analysis of these patients showed low and delayed 6-sulphatoxymelatonin excretion (<14 µg per night compared with 25 µg per minute in young adults). The study protocol consisted of two treatment periods of three weeks each, with one week wash-out interval between the two treatment periods. During the treatment periods, patients were administered orally either 2 mg controlled-release melatonin tablets, or placebo, two hours before bedtime. Five patients continued the melatonin treatment for a period of two months beyond the initial experimental period.

Patients' sleep was objectively assessed at the end of each treatment period for three consecutive nights using a wrist-worn actigraph. Motion recordings were analysed using the Neurim algorithm to determine sleep latency, sleep efficiency, total slepp time, wake after sleep onset and number of awakenings, as

an average over three nights for each subject. Six Wilcoxon matched-pairs signed-ranks analyses revealed statistically significant differences in sleep parameters between the melatonin and placebo treatment periods' ranks. The results are shown in Table 5.

Table 5: Effect on sleep parameters of melatonin replacement of benzodiazepine drugs.

Parameter	after 3 weeks' treatment melatonin	placebo	after +two months melatonin treatment
sleep efficiency)	82% (z = -2.82, p = 0.005)	75%	85%
sleep latency	17 mins. (z = -2.12, p = 0.03)	39 mins.	7 mins.
wake after sleep onset)	59 mins. (z = -2.00, p = 0.04)	76 mins.	42 mins.
no. of awakenings	11 (z = -2.70, p = 0.007)	17	10
total sleep time	386 mins. (z = -0.57, p = 0.58)	375 mins.	348 mins.

From the above results, it is concluded that melatonin replacement therapy can improve sleep initiation and maintenance in benzodiazepine drug-using elderly patients having a low endogenous melatonin output. The benefits of melatonin treatment increase with time, suggesting that reorganisation of the circadian system has occurred.

CLAIMS

1. Use of melatonin in the manufacture of a medicament for treating a multidrug addict, or a patient who has symptoms of having become dependent on, tolerant of, or addicted to a benzodiazepine drug, or for treating a patient who has been clinically diagnosed as having a condition susceptible to alleviation by administration of a benzodiazepine drug, while simultaneously preventing the occurrence in the patient of symptoms of dependence on, tolerance of, or addiction to said benzodiazepine drug.

2. Use according to claim 1, wherein said medicament comprises a pharmaceutical formulation adapted for oral, rectal, parenteral or transdermal administration and which comprises at least one diluent, carrier or adjuvant.

3. Use according to claim 2, wherein said pharmaceutical formulation is additionally characterized by at least one of the following features:

(i) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 0.0025-100 mg;

(ii) it is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate;

(iii) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier.

4. Use according to either claim 2 or claim 3, wherein said pharmaceutical formulation comprises also at least one benzodiazepine drug.

5. Use according to claim 4, wherein said benzodiazepine drug comprises at least one of Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Flunitrazepam, Flurazepam, Halazepam, Lorazepam, Oxazepam, Prazepam, Temazepam and Triazolam.

6. A pharmaceutical formulation, for use in treating a multidrug addict, or a patient who has symptoms of having become dependent on, tolerant of, or addicted to a benzodiazepine drug, or for treating a patient who has been clinically diagnosed as having a condition susceptible to alleviation by administration of a benzodiazepine drug, while simultaneously preventing the occurrence in the patient of symptoms of dependence on, tolerance of, or addiction to said benzodiazepine drug, which comprises at least one diluent, carrier or adjuvant and as active ingredients a benzodiazepine drug and melatonin.

7. A pharmaceutical formulation according to claim 6, which is adapted for oral, rectal, parenteral or transdermal administration, and which is further characterized by at least one of the following features:

(i) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 0.0025-100 mg;

(ii) it is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate;

(iii) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier.

8. A pharmaceutical formulation according to either claim 6 or claim 7, wherein said benzodiazepine drug comprises at least one of Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Flunitrazepam, Flurazepam, Halazepam, Lorazepam, Oxazepam, Prazepam, Temazepam and Triazolam.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 96/00082

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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T	JOURNAL OF PINEAL RESEARCH, vol. 20, no. 2, 1996, pages 65-71, XP002004027 J. ATSMON ET AL.: "RECIPROCAL EFFECTS OF CHRONIC DIAZEPAM AND MELATOIN ON BRAIN MELATONIN AND BENZODIAZEPAPINE BINDING SITES" see the whole document ---	1-8
X	EP,A,0 513 702 (IFLO-ISTITUTO FARMACOLOGICO) 19 November 1992 see abstract see page 3, line 32 - page 4, line 28 see page 4, line 50 - page 6, line 55; claims; examples --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Hoff, P

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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